

METHOD AND APPARATUS FOR LOCALIZING

BIOMAGNETIC SIGNALS

Technical Field

5 **[0001]** The invention relates to the measurement of magnetic fields generated by biological activity (biomagnetic signals). The invention has application to the localization of sources in magnetic imaging of biological structures. Some embodiments of the invention are used to provide continuous head localization information in
10 magnetoencephalography.

Background

[0002] Magnetoencephalography (“MEG”) involves detecting magnetic fields produced within a subject’s brain. Information about
15 such biomagnetic fields is most useful when it can be associated with particular structures within the subject’s brain. One can localize the subject’s head relative to the measured magnetic fields. To do this, the position of the subject’s head relative to the magnetic detectors used to detect the magnetic fields must be known.

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[0003] One way to localize a subject’s head is to attach small coils at three or more known locations on the subject’s head. The coils create fluctuating magnetic fields when alternating electrical currents are passed through them. Magnetic detectors are used to detect the coils’ magnetic
25 fields. The location of the coils, and thus the location of the subject’s head, can be determined from the detected magnetic fields of the coils.

[0004] One problem with some current head localization systems is that the coils generate large magnetic fields that can saturate the very sensitive magnetic field detectors used to detect biomagnetic signals. Because of this, head localization cannot be performed while

5 biomagnetic signals are being measured. With such current systems it is necessary to perform head localization before and/or after acquiring data about the biomagnetic signals. Such systems assume that the position of the subject's head changes predictably and can be determined from its positions before and/or after the biomagnetic signals are measured. These

10 assumptions are not always accurate.

[0005] Acquiring biomagnetic signals is often performed over significant time spans. During these times a subject's head is likely to move even if the subject is attempting to stay still.

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[0006] Magnetic noise can exacerbate the problems with head localization. The magnetic detectors used to detect the magnetic fields from the coils will also pick up noise signals, such as signals at the power line frequency (generally 60 Hz in North America and 50 Hz in

20 Europe) and at harmonics of the powerline frequency. Such noise signals can degrade the accuracy with which the positions of each of the coils can be determined. Magnetic noise includes environmental background noise, noise resulting from operation of the magnetic detectors and other components in the signals from the magnetic detectors which do not arise

25 from the magnetic fields of the coils.

[0007] There is a need for systems which permit continuous localization of heads and other structures during the acquisition of biomagnetic signals. There is a particular need for such systems which are relatively insensitive to noise.

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Summary of the Invention

[0008] This invention relates to localizing sources of biomagnetic signals. One aspect of the invention provides a method for locating an object relative to an array of magnetic sensors in an environment in
10 which there is present a noise signal having a fundamental frequency f_{NOISE} , the method comprising generating one or more magnetic signals by means of one or more magnetic emitters mounted at known locations on the object, the one or more magnetic signals having one or more frequencies; during an integration time T , detecting the one or more
15 magnetic signals and the noise signal at six or more magnetic detectors; and, determining relative amplitudes of the magnetic signals; wherein the one or more frequencies of the magnetic signals are substantially equal to frequencies at which a power spectrum of the detected noise signal has zeros.

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[0009] Further aspects of the invention and features of specific embodiments of the invention are described below.

Brief Description of the Drawings

25 [0010] In drawings which illustrate non-limiting embodiments of the invention,

Figure 1 is a schematic diagram of a MEG system which performs head localization according to one embodiment of the invention; and,

Figure 2 is a flow chart which illustrates a method for locating an object relative to an array of magnetic sensors according to another
5 embodiment of the invention.

Description

[0011] Throughout the following description, specific details are set forth in order to provide a more thorough understanding of the
10 invention. However, the invention may be practiced without these particulars. In other instances, well known elements have not been shown or described in detail to avoid unnecessarily obscuring the invention. Accordingly, the specification and drawings are to be regarded in an illustrative, rather than a restrictive, sense.

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[0012] Figure 1 shows a MEG system **20** according to one embodiment of the invention. System **20** includes a number M of magnetic detectors **24** which are located to detect magnetic fields originating within the head of a subject **S**. While Figure 1 represents a
20 detector array by only a few detectors **24**, a MEG system typically has a few hundred detectors **24**. Detectors **24** may be SQUID detectors. Signals from detectors **24** are appropriately conditioned by way of suitable signal conditioning circuitry **26**. The processed signals are provided to a signal processing system **28**. Signal processing system **28** generates output at an
25 output device **30**. The output may comprise, for example, a graphical display, a data file containing MEG data, or the like.

[0013] Coils 32, 33 and 34 are attached to the subject's head and are respectively driven with signals of frequencies f_1 , f_2 and f_3 (collectively referred to as f_q) by a controller 36 which, in the illustrated embodiment includes oscillators 37, 38, and 39. Driving signals for coils
5 32, 33 and 34 may be obtained in any suitable manner.

[0014] The location of any one of coils 32, 33 and 34 can be determined in standard ways if the amplitudes of the magnetic signals produced by the coil at a sufficient number of detectors 24 is known.
10 This invention provides a novel noise-insensitive mechanism for finding these amplitudes. The detectors 24 used for locating the coils may be the same detectors used to obtain MEG data. The detectors may be used simultaneously to obtain MEG data and to obtain information used to locate the coils.

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[0015] Detectors 24 are sampled periodically to provide a sequence of samples. The sequence of samples is acquired at a sampling rate sufficient to detect the signals from the coils. The sampling frequency is typically at least twice, and preferably at least four times the highest coil
20 frequency. Sampling is performed during an integration time, T . The integration time T is selected so the signals from the coils 32, 33, 34 can be separated from each other and from background noise. Ideally, when the output of detectors 24 is integrated over the integration time, signals at the noise frequency will integrate to zero over the integration time.
25 The integration time is selected based upon the expected frequency of noise.

- [0016] Since the position of a subject's head must be updated frequently, the integration time must be short, and this results in "spectral leakage" where the measurement of a head-coil signal at one frequency is affected by signals from the other head coils at other frequencies and/or by background noise. Spectral leakage can be reduced by multiplying the outputs of detectors **24** by a taper function in the integrations, and by selecting coil frequencies to be frequencies that do not interfere with each other.
- 10 [0017] Since the detectors are sampled over finite integration times, the locations of the zeros in the noise power spectrum depends upon the shape of the taper function, if any, applied to the samples. The examples discussed herein relate to the special case where the taper function is a "boxcar" (i.e. all of the samples in the integration time T are weighted
- 15 equally) and the noise environment is dominated by signals at a single frequency f_{NOISE} and its harmonics. The locations of the zeros will differ if other taper functions are used. If a taper function other than a boxcar is used then the coil frequencies may be selected to be at zeros of the power spectrum of the expected noise signal convolved with the taper function.
- 20 The issue of separating signals and spectral leakage with finite integration times T is discussed in many signal-analysis references, for example "Random data: Analysis and Measurement Procedures" by J.S. Bendat and A.G.Piersol.
- 25 [0018] Figure 2 is a flowchart illustrating a method **100** according to one embodiment of the invention. After method **100** begins at block **102**, magnetic signals are generated at block **104**. The magnetic signals

are generated by means of magnetic emitters, which preferably comprise coils. At block 106, the magnetic signals and the noise are measured by detectors 24. At block 108, the relative amplitudes of the magnetic signals are determined, as described further below.

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[0019] Where the frequency of the noise signal is f_{NOISE} , and a boxcar taper function is used, then suitable integration times T satisfy the formula:

$$T = \frac{N_1}{f_{NOISE}} \quad (1)$$

10 where N_1 is an integer and $N_1 \geq 2$. For example, if the noise fundamental frequency f_{NOISE} is 60 Hz then the integration time may be selected to be $N_1/60$ seconds. If $N_1=4$ then an integration time of 1/15 second is used. If the noise fundamental frequency is 50 Hz then the integration time may be selected to be $N_1/50$ seconds. If $N_1=5$ an integration time of 1/10
15 second is used. The integration time is preferably chosen to be short relative to any likely motions of the subject's head.

[0020] The coil frequencies f_1, f_2 and f_3 are selected to be different from one another and at or near frequencies to which the noise
20 fundamental frequency and its harmonics cannot spread, which are referred to herein as ideal coil frequencies f_{qi} . Ideally, each coil frequency f_{qi} satisfies the formula:

$$f_{qi} = \frac{N_2}{T} = \frac{N_2 \times f_{NOISE}}{N_1} \quad (2)$$

Where N_2 is an integer that is not a multiple of N_1 . For example, where the noise fundamental frequency is 60 Hz and $N_1=2$ then Equation (2) yields frequencies 30Hz, 90Hz, 150Hz, 210Hz ... etc. In preferred embodiments, the coil frequencies are chosen so that they will not
5 interfere with MEG measurements being made. It is also desirable to maintain the coil frequencies low enough that currents induced in the subject by the fluctuating magnetic fields of the coils are too small to interfere significantly with the coil signals. For example, in some MEG studies, the MEG signals of interest have frequencies of about 10Hz. In
10 such cases, the coil frequencies may be chosen to be sufficiently large that the lowest coil frequency is significantly higher than the frequencies of MEG signals to be studied. Typically the coil frequencies are in the range of 25Hz to 275 Hz. Higher coil frequencies could also be used. As another example, if a user is interested in MEG signals having
15 frequencies in the range of 70 -330Hz, the user could choose $N_1=8$ and $N_2 = 3, 5, 7$. This choice of N_2 yields coil frequencies of 22.5, 37.5 and 52.5Hz. In this example, the user would need to filter power line noise signals (including harmonics) which are within the range of frequencies of the MEG signals being studied.

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[0021] The complex amplitude, A_q^m , of the signal from the q^{th} coil at the m^{th} detector 24 can be determined from the set of samples S_k^m acquired over an integration period at the m^{th} detector by computing the sum:

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$$A_q^m = \frac{2}{N} \left[\sum_{k=0}^{N-1} S_k^m \cos(2\pi k f_q / f_s) - i \sum_{k=0}^{N-1} S_k^m \sin(2\pi k f_q / f_s) \right] = R_{qm} + i I_{qm} \quad (3)$$

where f_q is the frequency of the q^{th} coil, f_s is the detector sample rate, $N=Tf_s$ and k is an index indicating the order of the samples in the sequence of samples from each of the magnetic detectors. For locating the coils it is only necessary to obtain the relative amplitudes (including sign) of the signals from each coil at the different detectors (the complex phase of the signal from each coil is not important). A simple way to obtain the relative amplitudes of the signals is to use a detector which detects a strong signal (for example, the detector which detects the strongest signal) to establish the phase. If detector m_0 has the strongest signal at frequency f_q then the real relative amplitudes of the signals can be given by:

$$R_q^m = \text{Re} \left(A_q^m \times \frac{|A_q^{m_0}|}{A_q^{m_0}} \right) \quad (4)$$

[0022] Equation (4) is sufficiently accurate as long as the coil signals detected by at least a few of detectors **24** are strong enough that noise does not cause significant errors in the phases of the detected signals. More sophisticated techniques for obtaining the relative real amplitudes of the coil signals could be used but are usually unnecessary. For example, a least squares best estimate of the phase, ϕ_q , and relative real amplitude, R_q^m , of the coil signal of coil q could be obtained as follows:

$$\tan(2\phi_q) = \frac{2 \sum_m I_{qm} R_{qm}}{\sum_m (R_{qm}^2 - I_{qm}^2)} \quad (5)$$

and,

$$R_q^m = \text{Re}\left((R_{qm} + iI_{qm})e^{-i\phi_q}\right) \quad (6)$$

[0023] In some cases one or more of the frequencies f_1, f_2 and f_3 of the coil signals may not be exactly equal to the ideal frequencies f_{qi} identified by Equation (2). This could occur, for example, if the circuits used to drive the coils provide limited choice of coil frequencies. In such cases one should still use the ideal frequencies f_{qi} in Equation (3) and not the actual frequencies of the coil signals. To obtain the best accuracy in cases where the frequencies f_1, f_2 and f_3 of the coil signals are not exactly equal to the ideal frequencies identified by Equation (2) one should compensate for spectral leakage from the signals of the other coils.

[0024] In cases where one or more of the coil frequencies is not ideal, it is desirable that the actual frequencies of the coil signals be related to ideal frequencies of the coil signals by the following inequality:

$$\sqrt{(f_1 - f_{1i})^2 + (f_2 - f_{2i})^2 + (f_3 - f_{3i})^2} \leq \frac{1}{2T} \quad (7)$$

20 Where equation (7) is satisfied, the actual coil frequencies are “substantially equal” to the ideal coil frequencies. It can be seen that equation (7) will be satisfied if none of the coil frequencies departs from a corresponding ideal frequency by more than approximately $\frac{0.3}{T}$.

[0025] To compensate for spectral leakage that occurs when non-ideal coil frequencies are used, one can define the functions G_C and G_S as follows:

$$\begin{aligned} G_C(f_q, f_{qi}) &= \frac{2}{T} \int_{-\frac{T}{2}}^{\frac{T}{2}} \cos(2\pi f_q t) e^{-i2\pi f_{qi} t} dt \\ &= \frac{\sin(\pi(f_q - f_{qi})T)}{\pi(f_q - f_{qi})T} + \frac{\sin(\pi(f_q + f_{qi})T)}{\pi(f_q + f_{qi})T} \end{aligned} \quad (8)$$

5 and,

$$\begin{aligned} G_S(f_q, f_{qi}) &= \frac{2i}{T} \int_{-\frac{T}{2}}^{\frac{T}{2}} \sin(2\pi f_q t) e^{-i2\pi f_{qi} t} dt \\ &= \frac{\sin(\pi(f_q - f_{qi})T)}{\pi(f_q - f_{qi})T} - \frac{\sin(\pi(f_q + f_{qi})T)}{\pi(f_q + f_{qi})T} \end{aligned} \quad (9)$$

where f_{qi} is the ideal frequency closest to f_q . The real and imaginary parts C_q and S_q of the amplitudes measured at ideal frequencies f_{qi} can be related to the real and imaginary parts R_q and I_q of the true head coil amplitudes by way of the matrix equations:

$$\begin{bmatrix} C_1 \\ C_2 \\ C_3 \end{bmatrix} = \begin{bmatrix} G_C(f_1, f_{1i}) & G_C(f_2, f_{1i}) & G_C(f_3, f_{1i}) \\ G_C(f_1, f_{2i}) & G_C(f_2, f_{2i}) & G_C(f_3, f_{2i}) \\ G_C(f_1, f_{3i}) & G_C(f_2, f_{3i}) & G_C(f_3, f_{3i}) \end{bmatrix} \times \begin{bmatrix} R_1 \\ R_2 \\ R_3 \end{bmatrix} \quad (10)$$

and,

$$\begin{bmatrix} S_1 \\ S_2 \\ S_3 \end{bmatrix} = \begin{bmatrix} G_S(f_1, f_{1i}) & G_S(f_2, f_{1i}) & G_S(f_3, f_{1i}) \\ G_S(f_1, f_{2i}) & G_S(f_2, f_{2i}) & G_S(f_3, f_{2i}) \\ G_S(f_1, f_{3i}) & G_S(f_2, f_{3i}) & G_S(f_3, f_{3i}) \end{bmatrix} \times \begin{bmatrix} I_1 \\ I_2 \\ I_3 \end{bmatrix} \quad (11)$$

The simple form of equations (10) and (11) as a pair of 3x3 matrix equations can be achieved by expressing the integration time as the interval $-T/2 \leq t \leq T/2$. Equations (10) and (11) can be replaced with an equivalent single 6x6 matrix equation or an equivalent single 3x3 matrix equation in which the variables and coefficients have complex values. Equations (10) and (11), or their mathematical equivalents, may be applied to obtain corrected amplitudes to compensate for the coil frequencies not being exactly at the ideal frequencies described above.

10 **[0026]** Motion of the head coils will result in a time-varying signal amplitude, which in turn will cause spectral leakage such that the signal from one head coil affects the measurement of the amplitude of the signals from the other head coils, even if the coils are operated at the ideal frequencies specified in equation (2). Where the integration time is short enough that the signal amplitude can be modelled as a quadratic function, the spectral leakage can be considered to be a function of frequency separation only. Spectral leakage due to motion of the coils decreases with increased separation between the frequencies f_1 , f_2 and f_3 . It is desirable to maintain a spacing of, for example, 30 Hz or more, between all pairs of f_1 , f_2 and f_3 to minimize spectral leakage.

25 **[0027]** It can be appreciated that selecting coil frequencies as described above is a special case of a more general method. In general, the coil frequencies are selected to be equal to or substantially equal to those frequencies at which the power spectrum of the noise signal is zero. In this context, “substantially equal” is defined in equation (7) above.

Frequencies which are all within about $\frac{0.3}{T}$, where T is the integration time, of the corresponding ideal frequencies are substantially equal to the ideal frequencies. This is typically close enough to compensate for errors which arise from the coil signals not being at the ideal frequencies
5 by using, for example, equations (10) and (11).

[0028] Standard techniques may be used to determine the locations of each of the coils based upon the amplitudes determined above. Some suitable head localization algorithms are described in de Munck et al.,
10 Phys. Med. Biol. 46 (2001) pp. 2041-2052. For example, one way to determine the positions of the coils can be used in the case in which the coils are each small enough to be considered a point source and the detectors are magnetometers or first order gradiometers. It can be shown that the position \vec{y} can be determined by finding a value for \vec{y} which
15 minimizes the function H where:

$$H(\vec{y}) = \sum_k (\vec{m}(\vec{y}) \cdot \vec{C}_k(\vec{y}) - s_k)^2 = \vec{m} \vec{A} \vec{m} - 2 \vec{b} \cdot \vec{m} + \sum_k s_k^2 \quad (12)$$

where

- $\vec{m}(\vec{y})$ is the best-fit estimate of the source magnetic moment if the
20 source is at point \vec{y} . It is related to matrix \vec{A} and vector \vec{b} by

$$\vec{m}(\vec{y}) = \vec{A}^{-1} \vec{b}$$

Matrix \vec{A} and vector \vec{b} are functions of \vec{y} and are defined below;

- s_k is the amplitude of a the signal from a coil in the k^{th} detector;

- $C_{k\mu}(\bar{y})$ is the response of sensor k to a magnetic source located at point \bar{y} with moment of unit strength and oriented in spatial direction μ . $C_{k\mu}(\bar{y})$ may be represented as a power series in \bar{y} and the parameters that describe sensor k , or it may be expressed as an analytic function of the same variables;
- Matrix \vec{A} is a function of source point \bar{y} . The components of \vec{A} are $A_{\mu\nu} = \sum_k C_{k\mu}(\bar{y})C_{k\nu}(\bar{y})$;
- Vector \vec{b} is a function of source point \bar{y} . The components of \vec{b} are $b_\nu = \sum_k s_k C_{k\nu}(\bar{y})$.

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[0029] It is not necessary to use the signals detected at all detectors to determine the locations of each of the coils. It is generally acceptable to use signals detected at a subset of the detectors. Acceptable results can generally be obtained using coil signals detected at 30 or fewer properly chosen detectors. In some embodiments of the invention coil signals from 12 to 15 detectors are used to determine the position of each coil. It is not necessary that the same subset of coils be used to determine the positions of all of the coils. Indeed, it is desirable to use a different subset of the detectors for determining the position of each of the coils.

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20 Since the coils are expected to be in positions which are roughly known one could establish a predetermined subset of detectors to use for each coil.

[0030] A subset of the magnetic detectors to use for determining the position of a coil may be identified in various ways. In general it is desirable to include in the subset detectors having outputs which vary strongly with the position of the coil relative to the detector. In some
5 embodiments of the invention multiple criteria are used to select detectors in the subset. For example, in some embodiments, some detectors are included in the subset because they have relatively large signals from the coil and other detectors are included in the subset because the coil signal that they detect has a large variation with coil
10 position.

[0031] One algorithm for selecting detectors to include in the subset for a coil involves the following steps:

- Determine a number M_f of detectors to use for the fit. M_f may be
15 predetermined. M_f in the range of 12 to 15 is generally sufficient. M_f must be at least 6. More detectors may be required for coils which are relatively far from the closest detectors.
- Sort the detectors in order of the amplitude of the signal detected from the coil. Select the M_{fp} detectors having the largest signals for
20 inclusion in the subset. M_{fp} may be, for example, $2N/3$. In general M_{fp} may be any significant fraction of M_f (i.e. a fraction greater than about $1/3N$).
- Calculate an indicator, V , of the variation in the signal with coil position for each detector and include in the subset the $M_f - M_{fp}$
25 detectors having the largest values of V . Various functions can be used as the indicator. For example, in some embodiments, V is given by:

$$V = \frac{|s_m - s_{\max}|}{\left| \begin{matrix} \vec{r}_m & \vec{r}_{\max} \end{matrix} \right|} \quad (13)$$

where s_{\max} is the amplitude of the signal at the detector having the largest signal from the coil and \vec{r}_{\max} is the location of the detector having the largest signal from the coil.

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[0032] Information about the coil positions may be used in various ways. For example, the coil positions may be monitored in real time and compared to reference positions. Suitable action may be taken based upon the coil positions. For example:

- 10 • an alarm may be triggered if the coil positions are determined to be too far away from the reference positions;
- data may be discarded for those times during which the coil positions are determined to be too far away from the reference positions;
- 15 • a sensory (e.g. visual, audible or tactile) feedback indicator may be provided to help subjects keep their heads in a desired position;
- the positions of the coils may be recorded along with MEG data for later correction of the MEG data to account for motion of the subject's head;
- 20 • the MEG data may be corrected in real time to correct for motions of the subject's head. One way to correct the MEG data is described in the co-pending commonly owned patent application entitled MOTION COMPENSATION IN BIOMAGNETIC MEASUREMENT being filed together herewith, which is hereby
- 25 incorporated by reference herein.

[0033] Certain implementations of the invention comprise computer processors which execute software instructions which cause the processors to perform a method of the invention. For example, one or
5 more processors in a controller for a MEG system may implement a method of Figure 2 by executing software instructions from a program memory accessible to the processor(s). The invention may also be provided in the form of a program product. The program product may comprise any medium which carries a set of computer-readable signals
10 comprising instructions which, when executed by a computer processor, cause the data processor to execute a method of the invention. Program products according to the invention may be in any of a wide variety of forms. The program product may comprise, for example, physical media such as magnetic data storage media including floppy diskettes, hard disk
15 drives, optical data storage media including CD ROMs, DVDs, electronic data storage media including ROMs, flash RAM, or the like or transmission-type media such as digital or analog communication links.

[0034] Where a component (e.g. a software module, processor,
20 detector, assembly, device, circuit, etc.) is referred to above, unless otherwise indicated, reference to that component (including a reference to a "means") should be interpreted as including as equivalents of that component any component which performs the function of the described component (i.e., that is functionally equivalent), including components
25 which are not structurally equivalent to the disclosed structure which performs the function in the illustrated exemplary embodiments of the invention.

[0035] As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. For example:

- In the above description, a number of coil signals are monitored simultaneously. In alternative embodiments of the invention the coil signals are time multiplexed. In this case, the coil signals may be at the same frequency or at different frequencies. The coil frequency or frequencies are chosen to be frequencies at which the power spectrum of the expected noise signal convolved with any taper function being applied has zeros.
- The foregoing discussion assumes that the magnetic signals generated by the coils are each at a single fixed frequency and remain uniform in frequency and amplitude over the integration period. In general, this is not necessary.
- Magnetic detectors **24** may be of any suitable types. For example, detectors **24** could be magnetometers or first or second order magnetic gradiometers. Detectors **24** could be SQUID magnetometers or gradiometers.
- While the invention is discussed above in the context of a MEG system, the invention may be applied to locating other objects oscillating magnetic fields relative to an array of magnetic sensors.
- While the mathematical formulae presented herein have been structured to avoid the need for computations using complex numbers, one could perform equivalent calculations using complex

numbers at the expense of somewhat greater memory usage and somewhat slower calculation.

Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.